

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Cornelis Marius Timmers

Application No.: 10/540,335

Confirmation No.: 8737

Filed: January 10, 2006

Art Unit: 1623

For: TETRAHYDROQUINOLINE DERIVATIVES AND Examiner: Bland, Layla D.
THEIR USE AS FSH RECEPTOR MODULATORS

DECLARATION UNDER 37 C.F.R. § 1.132

I, CORNELIS MARIUS TIMMERS, of Boterbloem 26, 5351 MV, Berghem,

The Netherlands, declare as follows:

I. BACKGROUND

1. I am a named co-inventor of U.S. application Serial No. 10/540,335 ("the '335 application") filed January 10, 2006.

2. I received my PhD degree in 1997 from Leiden University, The Netherlands. Since 1997, I have worked for Organon as (senior) research scientist. I am currently Organon's senior director Lead Optimization. In that position, I am responsible for providing medicinal chemistry support to various project teams in research.

3. I have reviewed and understood the specification and claims of U.S. patent application Serial No. 10/540,335 entitled "Tetrahydroquinoline Derivatives and Their Use as FSH Receptor Modulators".

II. TETRAHYDROQUINOLINE DERIVATIVES OF TO THE PRESENT APPLICATION

4. I have carefully reviewed the examples in the application describing the preparation of tetrahydroquinoline derivatives.

5. I have carefully reviewed the method of determining CHO-FSH bioactivity as described in the specification of the present application and as set forth in Example 44 of the specification. This determination of bioactivity (either as an agonist, antagonist or both) was also described in the specification on pages 16, line 17 to page 18, line 16.

6. The attached table (designated Table 1) accurately reflects the chemical structure of each of examples 1-42 and the bioactivity for each of these examples as obtained at the time the present application was filed. The term "FSH_AGOCHO EC50" in Table 1 reflects the EC50 value for agonist activity of the particular compound with respect to the FSH receptor which is expressed in CHO cells for the assay described in Example 44 of the specification. The term "FSH_ANTCHO EC50" in Table 1 reflects the EC50 value for antagonist activity of the particular compound with respect to the FSH receptor which is expressed in CHO cells for the assay described in Example 44 of the specification.

7. An EC50 value of less than $1.00E-5$ for FSH_AGOCH indicates that the particular compound in the table is considered to have agonist activity. An EC50 value of less than $1.00E-5$ for FSH_ANTCHO indicates that the particular compound in the table is considered to have antagonist activity. Some compounds in the table have an EC50 value of less than $1.00E-5$ for both FSH_AGOCHO and for FSH_ANTCHO and

these compounds are considered to have both agonist activity and antagonist activity at different concentrations of the particular compound, hence the difference in EC 50 values for these compounds comparing the values for FSH_AGOCHO and FSH_ANTCHO.

III. CONCLUSION

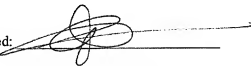
8. In summary, the attached Table 1 provides both structural information and bioactivity data for each of the compounds of examples 1 to 42 of the present application. These compounds are exemplary for the class of compounds described by formula 1 as in the present application and show either agonist activity, antagonist activity or both with respect to the FSH receptor according to the assay described.

9. I declare that all statements made herein are true, and that all statements made herein on information and belief are believed to be true, and that all statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that any willful false statement may jeopardize the validity of any United States Patent that would issued from the '335 application.

Dated:

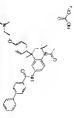
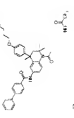
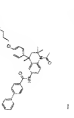
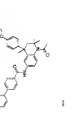
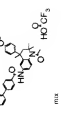
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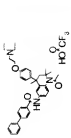
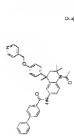
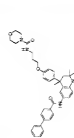
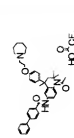
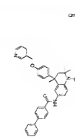
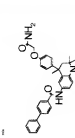
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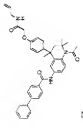
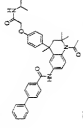
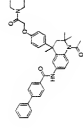
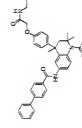
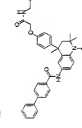
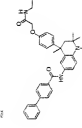


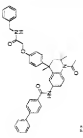
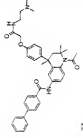
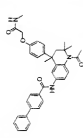
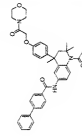
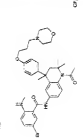
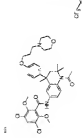
Cornelis Marius Timmers

TABLE 1

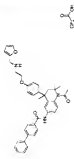
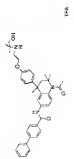
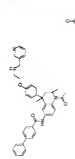
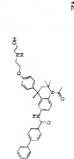
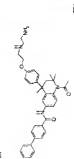
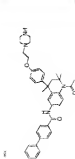
Ex#	STRUCTURE	FSH_AGOCHO EC50	FSH_ANTCHO EC50	R1, R2	R3	R4	R5
1		>e-5	1.90E-06	Me	R6-ethyl	biphenyl	dimethylamino
2		>e-5	2.30E-06	Me	R6-propyl	biphenyl	dimethylamino
3		> 1.00E-05	7.193E-08	Me	morpholino-propyl	biphenyl	
4		> 1.00E-05	2.580E-08	Me	2-pyridinyl-methyl	biphenyl	
5		>e-5	1.90E-06	Me	(1-methyl-piperidin-3-yl)-methyl	biphenyl	

6	 mix	>e-5	1.40E-06	Me	R6-ethyl	biphenyl	diethylamino
7	 --	> 1.00E-05	2.148E-08	Me	4-pyridinyl-methyl	biphenyl	
8	 --	> 1.00E-05	1.118E-07	Me	morpholino-carbonyl-amino-propyl	biphenyl	
9	 mix	>e-5	2.10E-06	Me	R6-ethyl	biphenyl	azepan-1-yl
10	 --	> 1.00E-05	2.272E-08	Me	3-pyridinyl-methyl	biphenyl	
11	 mix	>e-5	9.60E-08	Me	R6-carbonylmethyl	biphenyl	amino

12		> 1.00E-05	5.234E-08	Me	R6- carbonylmethyl	biphenyl	propenylamino
13		> 1.00E-05	9.499E-08	Me	R6- carbonylmethyl	biphenyl	isopropylamino
14		> 1.00E-05	6.00E-06	Me	R6- carbonylmethyl	biphenyl	diethylamino
15		> 1.00E-05	5.207E-07	Me	R6- carbonylmethyl	biphenyl	4-pyridinyl- methyl-amino
16		> 1.00E-05	8.830E-08	Me	R6- carbonylmethyl	biphenyl	2-furanyl- methylamino
17		> e-5	2.60E-07	Me	R6- carbonylmethyl	biphenyl	methoxy- ethylamino

18		>e-5	5.30E-06
19		>e-5	2.30E-06
20		>e-5	3.10E-07
21		>e-5	4.60E-07
22		5.60E-07	>e-5
23		1.90E-06	aff. <20%

Me	R6- carbonylmethyl	biphenyl	benzylamino
Me	R6- carbonylmethyl	biphenyl	dimethylamino- ethylamino
Me	R6- carbonylmethyl	biphenyl	methylamino
Me	morpholino- carbonyl methyl	biphenyl	
Me	morpholino propyl	5-bromo-2- methylamino- phenyl	
Me	morpholino propyl	3,5-dichloro- 2,6-dimethoxy phenyl	

24		> 1.00E-05	2.857E-07
25		> 1.00E-05	1.339E-06
26		> 1.00E-05	1.945E-07
27		> 1.00E-05	1.079E-06
28		> 1.00E-05	1.008E-06
29		> 1.00E-05	1.992E-06

biphenyl
 2-furanyl-
 methylamino

R6-ethyl

Me

biphenyl
 1-hydroxy-2-
 methyl (propan-
 2-yl)amino

R6-ethyl

Me

biphenyl
 3-pyridinyl-
 methyl-amino

R6-ethyl

Me

biphenyl
 hydroxyethyl
 amino

R6-ethyl

Me

biphenyl
 aminoethylamino

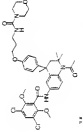
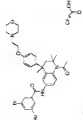
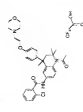
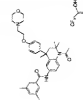
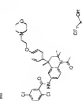
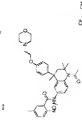
R6-ethyl

Me

biphenyl

ethylpiperazino

Me

30		2.88E-06	> 1.000E-05
31		6.52E-07	> 1.000E-05
32		4.57E-07	> 1.000E-05
33		1.09E-06	> 1.000E-05
34		1.68E-07	> 1.000E-05
35		7.69E-07	> 1.000E-05

Me morpholino-
carbonyl-
amino-propyl
3,5-dichloro-
2,6-dimethoxy
phenyl

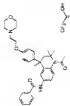
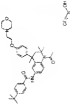
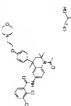
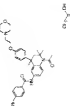
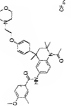
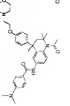
Me ethylmorpholino
3,5-dibromo
phenyl

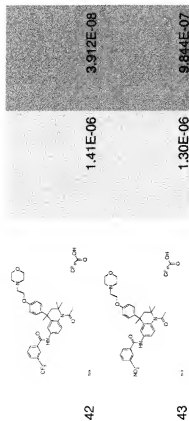
Me ethylmorpholino
2-
chlorophenyl

Me ethylmorpholino
3,5-dimethyl
phenyl

Me ethylmorpholino
2,5-dichloro
phenyl

Me ethylmorpholino
5-methyl-2-
nitro phenyl

36		> 1.00E-05	5.379E-08	Me	ethylmorpholino	phenyl
37		> 1.00E-05	3.945E-08	Me	ethylmorpholino	4-tert-Butyl phenyl
38		1.90E-07	> 1.000E-05	Me	ethylmorpholino	2,3-dichloro phenyl
39		> 1.00E-05	2.559E-08	Me	ethylmorpholino	5-bromo phenyl
40		>e-5	3.048E-07	Me	ethylmorpholino	4-methoxy-3- methyl phenyl
41		> 1.00E-05	1.669E-08	Me	ethylmorpholino	4- dimethylamino phenyl



Me ethylmorpholino
 3-trifluoromethyl
 phenyl

Me ethylmorpholino
 3-nitro phenyl